

The Idea:

The Vestibulocochlear working concept for PTSD

This summary of the vestibulocochlear theory for the development of PTSD is presented in response to the IRB (WRNMMC) scientific review being done for the study “High Definition Fiber Tracking of Chronic TBI: Analysis of a Cohort with Vestibulocochlear Injuries and Concomitant Posttraumatic Stress Disorder Manifestations” (IRBNet # [366913-1] on which the study is based. The elucidation of the vestibulocochlear concept in the proposal as it is reviewed has been written for a general audience and has prompted questions for clarifications from reviewers. This reference material on the vestibulocochlear concept for PTSD is intended to complement the proposal under review.

In introducing the vestibulocochlear concept for the development of PTSD in this study, we do not claim that it is the final solution for explaining PTSD. We are merely pointing out that there is already palpable and mounting evidence in the literature to support the theory and it is still untested. There are clearly other working theories which we have enumerated but their gaps in trying to explain PTSD do not necessarily mean that they will not be complemented by the vestibulocochlear theory if so tested. The bottom line is a better understanding of this complex disorder which admittedly, even from the ranks of the PTSD treatment providers, is mired with controversy regarding its pathophysiology^{1 2 3}. The geist of the vestibulocochlear theory for PTSD development is how injury through the neuroanatomical structures within the vestibulo-auditory pathway brings about PTSD . To arrive at a conceptual appreciation of the theory, we have set a sequence of topics to review: (I) the neuroanatomical setting in which this injury takes place (II) representative studies linking TBI, vestibulocochlear injury and PTSD (III) Peripheral and higher vestibular function and impairment (IV) Deafferentation injuries in the peripheral and central nervous system (V) The Amygdala as mediator between Hippocampus and Hypothalamus (VI) The role of Handedness in locating the dominant Vestibular Tract (VII) The DSM-IV PTSD criteria explained through the vestibulocochlear theory (VIII) Implications (IX) How do we test the vestibulocochlear working concept for the PTSD study?

I Neuroanatomical setting for vestibulocochlear injury

The Vestibulocochlear nerve Cranial Nerve(CN) VIII is a twinned nerve consisting of (a) the Auditory nerve and (b) the Vestibular nerve. Although sharing conjoined neuroanatomical space from its peripheral extent in the middle ear to its cortical (central) representation, its respective pathways take independent turns within the brain and the spinal cord making both pathways one of the most extensive cranial nerve network in the body. As we review this double pathway, we will be referring to the combined pathway as the vestibulocochlear (or vestibulo-auditory) pathway or separately as the: (1) auditory pathway and the (2) vestibular pathways.

Although there are a myriad of structures within the vestibulo-cochlear or vestibulo-auditory pathway, we will focus on the specific structures whose injury or dysfunction lead to the manifestations seen in PTSD. These are in 3 main areas:

A. Inner ear and vestibular – auditory nerve communication

Motor efferents from the crossed and uncrossed olivocochlear bundle of the brain stem enter the cochlea to modulate hearing and equilibrate auditory information between both ears to establish lateralization and location of the source of sounds^{4 5}. The vestibular nerve has also been identified with its own share of motor efferents from the brainstem flowing adjacent to the periolivary cell groups of superior olivary nucleus (cochlear) joining the auditory nerve⁵. From an outer ear inspection view, the eardrum is readily seen blocking the view of the semicircular canals. Injury to the eardrum (or tympanic membrane perforation) is evaluated as indirect evidence of labyrinthine (or semicircular canal) injury, specially if the mechanism of injury concerns Blast-induced events. Blast injuries are compounded in fluid-filled organelles such as the semicircular canals⁶, which can lead to functional or deafferentation injury to the vestibular nerve which is sensed through the whole vestibular network.

B. Brainstem vestibular nuclei linkages with

- (a) Cerebellum - A vestibular nuclei (Deiter's nucleus) loops around the flocculonodular lobule of the cerebellum (which takes care of "muscle memory" and automatic righting reflexes) before connecting with the remaining vestibular nuclei in the brainstem.
- (b) vestibulospinal tracts and righting reflexes – tract that connects the vestibular system to all 4 limbs subserving proprioceptive receptors
- (c) medial longitudinal fascicle and vestibulo-ocular reflexes – the main fiber tract in the pontomedullary area connecting the vestibular system with extra-ocular muscle function subserving the vestibulo-ocular reflex

C. Thalamo-cortical and Limbic connections

- (a) Parieto-insular vestibular cortex (PIVC) –the cortical representation of vestibular and related multisensory input from the Thalamus.
- (b) posterolateral thalamus - serves as the relay station for ipsi- and contralateral ascending vestibular input all the way to its central cortices in the insula where the vestibular (as the parieto-insular vestibular cortex) (PIVC) sits in the superior temporal gyrus (STG) adjacent to the Auditory center in Heschl's gyrus . Aside from the proximity of the Auditory center in the temporal lobe to the fornices which form part of the limbic system and sweeps forward to end in each mesial temporal lobe as hippocampi with its paired amygdala, Direct neural projections traced from the auditory somatosensory nuclei of the thalamus to the amygdala were found which ran in parallel with an indirect circuit running first to the auditory cortex before ending up in the amygdala⁸
- (c) Hippocampi(us) – because it relays position sense from its bilateral temporobasal position, it functions as part of the vestibular system; its hyperactivation in vestibular stimulation and decrease in size among PTSD patients have been documented in fMRI studies.
- (d) Midline structures:
 - i) Caudate nucleus – linked to motor activity, frontal eye fields also subserving the vestibulo-ocular reflex.

- ii) anterior cingulate cortex (ACC) – has regulatory function in emotional processing.
- iii) retrosplenial cortex – contextual association , associative multisensory learning and priming (traumatic re-experience).
- iv) Amygdala – the common trigger structure hyperactivated in many anxiety states; fMRI studies show dorsal and rostral cingulate hypoactivation only in PTSD; has abundant connections to and from hippocampus; directly signals hypothalamus.
- v) Hypothalamus – receives signals from the amygdala to initiate release of endocrine stress hormones and activates autonomic nervous system for “fight or flight” reaction.

In a recent study by Franke et al⁷ a potential vestibular tract arising from the posterolateral nucleus of the thalamus directly to the hippocampus has been postulated. This vestibular thalamo-hippocampal tract (between 4 and 7) forms the hypothesis behind the vestibulocochlear working concept for PTSD as can be appreciated from the series of downstream events that follow .

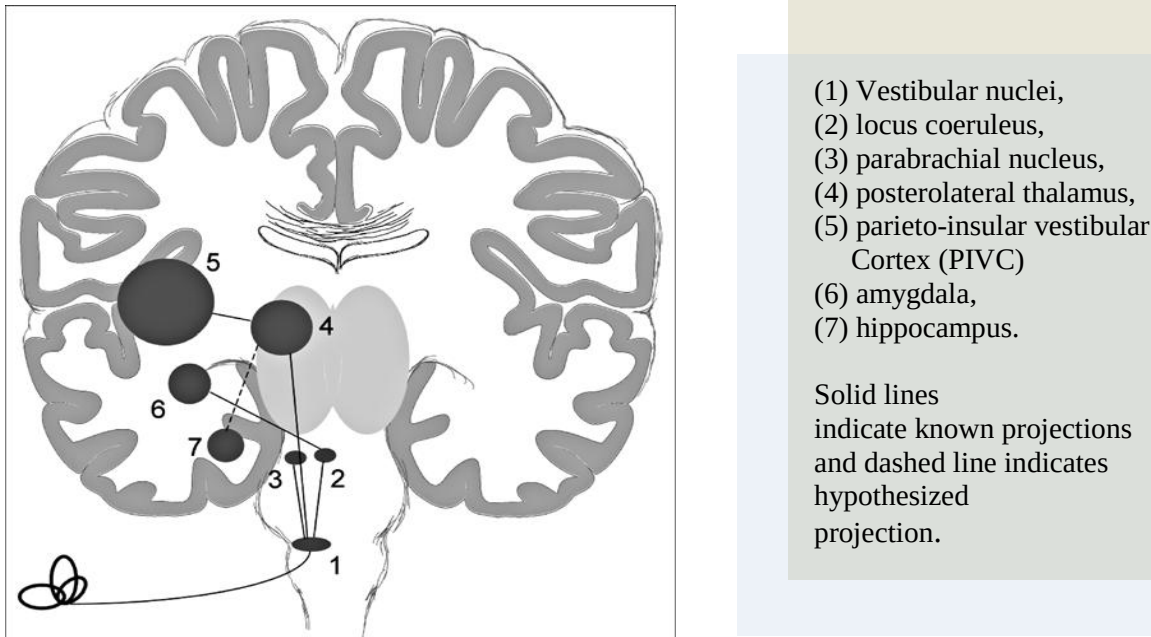


Fig 1 Posterior central nervous system projections of vestibular nuclei subserving spatial and emotional processing.

II. Representative studies linking TBI, vestibulo-cochlear injury and PTSD

Because the auditory nerve is closely linked to the vestibular nerve not only in its cortical representation (insula) but within the inner ear, auditory impairment or dysfunction such as deafness, tympanic membrane perforation and tinnitus give us indirect evidence of vestibular injury as well, although in moderate to severe impairment of the vestibular labyrinth, this vestibular impairment can be clinically observed as dizziness, vertigo or gait imbalance. Studies by Xydakis et al⁸ reported a prevalence of 35.2 % of blast injuries having tympanic membrane perforations. Fagelson⁹ working on 300 veterans with Tinnitus found 34% to have PTSD. Dizziness and deafness along with

disorientation have been the consistent presentations of Charles Myers¹⁰ earliest documentations of WWI patients with ‘shell shock’ from where we trace the origins of PTSD. These representative studies already depict different windows of focus into the problem of PTSD in time all supporting the concept that TBI, Blast injury and vestibulocochlear impairment are related. In testing this concept further, we compared our Head Injury OIF/OEF data with the past major wars from their available records^{11 12 13 14 15 16 17 18 19}.

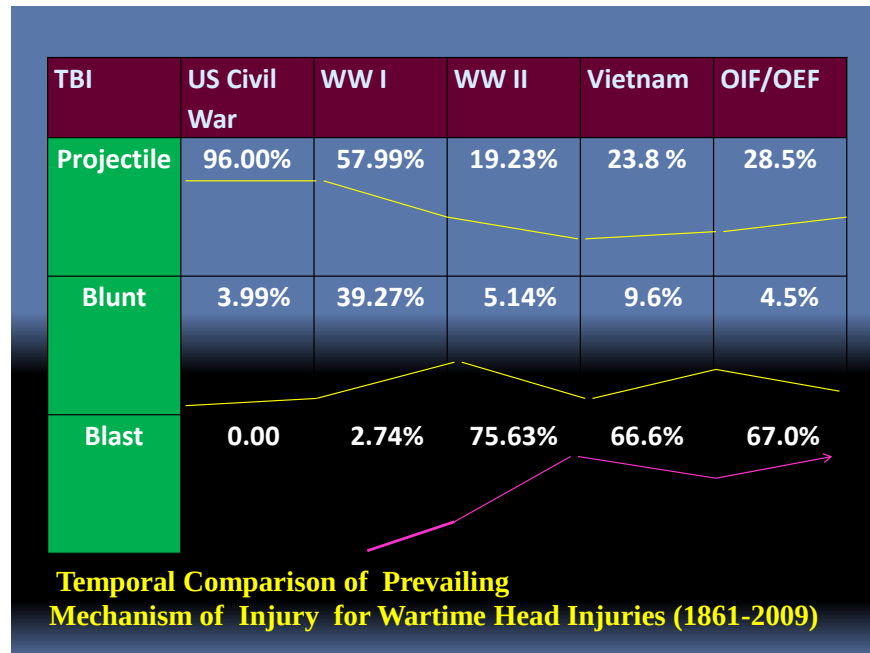


Diagram 1. The introduction of Blast weapons and consequent injuries traceable to WWI documentation of “shell shock”

Although the separate classification of vestibulocochlear damage and the non-categorization of PTSD (as in the DSM-IV criteria) in the previous world wars made evaluation in these areas unreliable, data on mechanisms of injury were comparable and informative in so far as correlating the beginnings of Blast injury with the timepoint when PTSD as “shell shock” was first documented.

III. Peripheral and Higher Vestibular Function and Impairment

Most of the clinically applied tests for vestibular function examine the integrity of the semicircular canals, the connections of the vestibular nerve to the righting reflexes involving the optokinetic (or eye-tracking) reflexes and cerebellar association (dysdiadokinesia, Romberg test) for posturography or assessment of balance. Although bodily integrated through the medial longitudinal fascicle and vestibulospinal tracts down to its proprioceptive receptors, these association fibers are traceable to the input of the vestibular nerve receiving the adequate stimuli from movement of the semicircular canals or labyrinth, an exteroceptive sensor. These vestibular functions emanating from the exteroceptive sensor we shall now classify as peripheral vestibular functions to distinguish them from the higher vestibular functions of navigation, self-motion and perception of verticality or global position sense integrated in the Parieto-Insular Vestibular Cortex

(PIVC) which have been cited to be difficult to test clinically²⁰. To define these higher vestibular functions further, we have:

Perception of verticality²¹ – to perceive oneself upright in space aligned with gravity or what we will call Global Position Sense as differentiated from weightless position in space.

Navigation²² - ability to update information from an inner self-referenced representation of space as one moves (input from ‘place cells’ in hippocampus and ‘grid’ cells in MEC)

Self-Motion²³ - a sense of self-movement which is dependent on the PIVC integration with the visual pathway. (strokes or lesions on the PIVC may remove the perception of vertigo even in the presence of nystagmus²⁴) which may be aided by auditory cues without vestibular stimulation as well as proprioceptive input from the kinematics of walking and haptic information from wind pressure²⁵.

IV Deafferentation Injuries in the Peripheral and Central Nervous System

To carry the explanation for functional injury or impaired nerve impulse transmission further; when nerves subserving pain and temperature are partially severed or deafferented, the causalgia or chronic pain at the affected limb or site results in hyperesthesia at the injured site regardless if a noxious stimuli or light touch is introduced²⁵. There is heightened sensation to compensate for the injury evidenced by the aversive withdrawal actions to light touch we witness. In the extreme case of complete nerve severance as in amputation, we see this heightened pain and sensory function as the thalamic projection of phantom pain. This phenomenon of compensatory or heightened function of adjacent and related neural structures have been used for neurorehabilitation of the chronic stroke limb by causing temporary functional deafferentation (TFD)^{26 27} of the good limb with anesthetic cream. In the peripheral nerve injury, there is an approximated 35% loss of neurons proximally while the distal axons undergo Wallerian degeneration. Carrying this process of nerve injury, repair and healing to the cortical level involving several association fiber tracts takes time. It is reported that the compensatory cortical representation of an adult primate’s amputated finger by the adjacent intact finger is registered around 2 months post-injury, about the same time PTSD becomes clinically manifest after a traumatic event²⁸. From the perspective of the vestibulocochlear working theory behind PTSD, the impairment that is registered mainly in the vestibular nerve leads to a functional injury (nerve neuroanatomically intact but physiologically unable to transmit nerve impulses normally) that affects the vestibular and its related circuitry (auditory nerve and tract) prompting an attempt at CNS reorganization in response to injury. Unlike the nerves which subserve pain and temperature function, the vestibular nerve has a kinesthetic function. Kinesthesia or the loss of it is a multisensory function. Therefore, compensation for this impairment will lead to heightening of the related visuo-tactile sensory tracts as well as its links to the limbic system. The consequent

clinical manifestation will be akin to the archival WWI films of soldiers suffering from “shell shock” manifesting not only gait ataxia but also the classic startle reflex and a restless hyperagitated state, depicting a kinesthetic vestibular system maladaptively reorganized.

In the case of the vestibular and auditory nerves’ intricate connections, this forms the neuroanatomical basis of two independent pathways being able to sense a functional impairment in one to compensate with an enhanced function of its adjacent tract. The visuo-tactile tracts which form linkages as inputs to the vestibular PIVC are also potential pathways by which this phenomenon of impairment and compensatory enhancement can be manifested.

The PIVC cannot be named a primary sensory area since it is in fact multisensory receiving visual, tactile as well as vestibular inputs. The impairment of higher vestibular functions seated at the PIVC involving navigation, self-motion and global position sense, results in a compensatory hyperfunction of the multisensory tracts linked to the PIVC reflecting the hypervigilant state we see in PTSD.

V The Role of the Hippocampus in Higher Vestibular Functions

The hippocampus has been more widely recognized to house memory function. Less popularly, its role in aiding position sense has not been given the attention it merits. In 1974, O’Keefe and Dostrovsky²⁹ were able to prove through electrode monitoring of the rat hippocampus the existence of ‘place cells’. Simply put, these were hippocampal neurons that fired when the rat arrived at exactly the same spot or location it had been while exploring its surroundings. The experiment in discovering ‘place cells’ had been replicated in a host of other mammalian animal models³⁰. Further tests had demonstrated “grid cells³¹” in the medial entorhinal cortex which fired impulses to the hippocampus in equally-spaced coordinates subserving a higher order vestibular function – that of global position sense. Through stroke studies³² involving hippocampal infarctions (reduplicative paramnesia), the position sense function of the hippocampus was further confirmed in humans. An article³³ assessing navigation with neuroimaging which challenged the hippocampal role in assessing position had to conclude that the hippocampus has a role in determining position. The study, which directed subjects to recall directions to familiar places under fMRI was flawed as the tasks assigned used motor (finger clicks) activity as responses which affected the neuroimaging results. Functional MRI studies by Vitte et al³⁴ showed activation of the hippocampus, together with the retrosplenial cortex and subiculum upon vestibular stimulation.

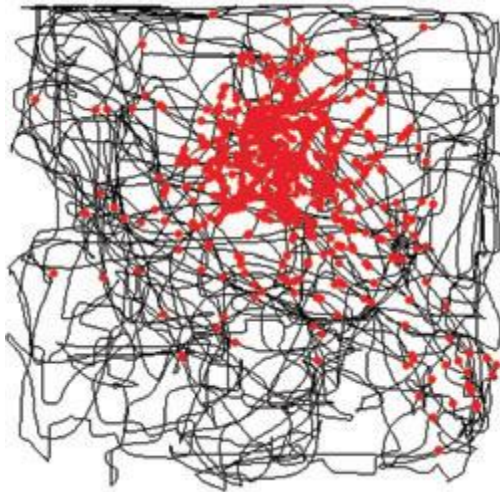
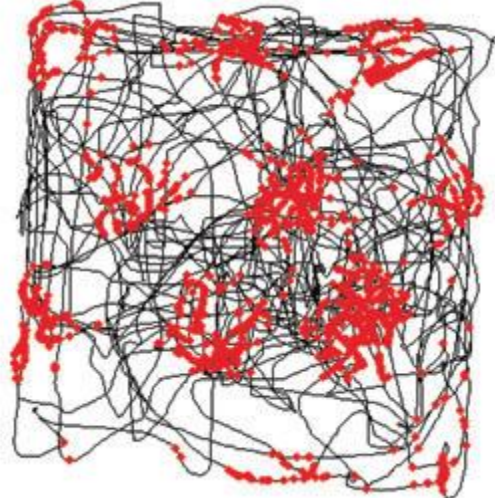


Fig. 2 The firing pattern of “Place” cells in the Hippocampus



The firing pattern of “Grid” cells in the medial entorhinal cortex (MEC)

(The wriggly gray lines depict the route taken by the rat model in exploring its environment and the red dots depict hippocampal and MEC neuron firing)

The added position and navigation function for the hippocampus in the context of other existing organelles or neural areas (vestibular labyrinth, cerebellum, vestibulospinal tract, PIVC) subserving similar functions begs the question: Are these structures not connected? This question has not been lost to investigators cited before (Franke et al⁷) who in analyzing sensorintegrative tracts for higher vestibular function postulated a vestibular nuclei to amygdala association tract through a connection relayed from the posterolateral thalamus to the hippocampus. The study had adopted this postulated association tract as its hypothesis when it was first written in 2011, thus completing a more understandable circuit for PTSD to manifest itself.

VI The Amygdala as mediator between Hippocampus and Hypothalamus

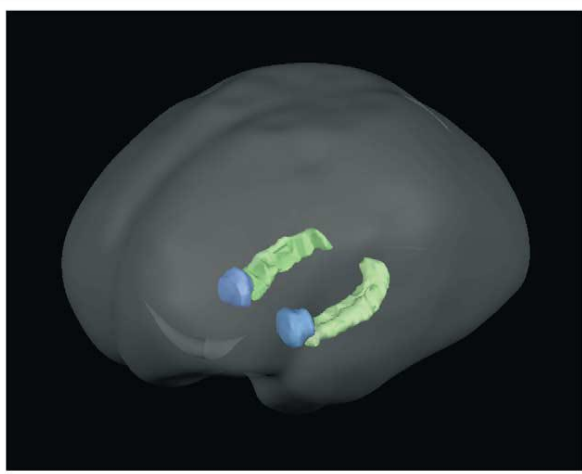


Fig. 3 The human amygdala (in blue) and hippocampus (in green). (from Phelps EA. “Human Emotion and Memory: Interactions of the Amygdala and Hippocampal Complex” *Current Opinion in Neurobiology* , 14:198–202, 2004

What is clear both from animal and human imaging studies^{35 36}, is that there are 2 independent memory systems at work when emotion meets memory : (1) emotional memory enhanced by the amygdala and (2) episodic working memory – stored by the hippocampus. This type of memory system is crucial for the acquisition and expression of fear conditioning wherein a neutral stimulus acquires aversive properties by virtue of being paired with an aversive event which is stored in the hippocampal complex. As memory goes through the stages of encoding, consolidation, storage and retrieval, the activity demonstrated by neurophysiologic and imaging studies show a bi-directional flow between hippocampus and amygdala wherein hippocampal encoding can be influenced by the amygdala (attenuation or enhancement of memory) and inversely, hippocampal-dependent memory can also influence amygdala function to produce hypothalamic-driven stress hormones even if the aversive event is only imagined or taken from stored hippocampal memes of aversive events. Several studies^{37 38} examining the neural substrates underlying our ability to regulate our emotional response demonstrated that the amygdala response might be altered by cognitive strategies, as we observe in PTSD patients undergoing Cognitive-based therapies (CPT, CBT or PE), showing an influence from hippocampal-dependent memory.

The amygdala has also reciprocal connections with sensory cortical processing regions, such as the visual cortex³⁹ or auditory cortex which provide it with adequate sensory stimuli to affect hippocampal encoding of aversive memories.

The vestibulocochlear working concept for the PTSD study defines this intimate interaction between hippocampal complex (to include the parahippocampus) and amygdala as an encoding-reappraisal-synchronization process wherein the signals that first alert the amygdala of danger are circuited back to the hippocampus as the emotive memory which will pair with the episodic memory stored in the hippocampus. This confirmatory synchrony is transmitted to the midline structures (anterior cingulate cortex(ACC) and retrosplenial cortex) for emotional processing and error monitoring. The feedback mechanisms of the anterior cingulate cortex have not been elucidated in detail in the literature but it is known that the rostral ACC is glutamatergic (excitatory) and that it connects with a number of limbic structures, to include the hippocampus and amygdala as this memory synchrony is evaluated to confirm error or non-error⁴⁰. The ACC has links to the retrosplenial cortex posteriorly which has dual functions for memory and visuospatial or proprioceptive function. The retrosplenial cortex has its largest projection going to the parahippocampal and entorhinal cortex and through reciprocal pathways involving the anterior and lateral thalamic nuclei, serve to connect the dorsolateral prefrontal cortex (DLPFC) with the hippocampal formation. Although the retrosplenial cortex, based on fMRI studies⁴¹, is often invoked as the site where recurrent and intrusive thoughts on the initial trauma are mediated for PTSD patients, little detail has been provided to support this further. Based on animal studies, its role is evaluative and fMRI literature confirms it as the most consistent of activated structures by emotionally salient stimuli⁴¹.

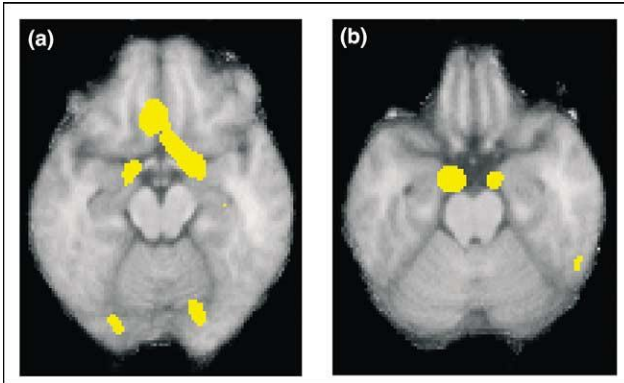


Fig. 4 Activation of the amygdala predicts later memory. Amygdala activity during encoding correlated with subsequent memory for (a) positive and (b) negative arousing picture stimuli. Adapted from Hamann et al, 1999)

When functional injury occurs in the vestibular nerve, the abnormal transmission of impulses from the deafferented area of the nerve affect the whole vestibular network , to include the posterolateral thalamus and enhances the hippocampal memory sites and ‘place’ cells through the postulated thalamo-hippocampal tract. In going through the encoding-reappraisal-synchronization process, the emotive memory formed in the amygdala is now unable to pair correctly with the episodic or contextual hippocampal memory site since the hippocampal complex and its memory sites are functionally rendered pathologic and non-recognizable for this pairing to occur. As an incorrectly paired emotive and contextual meme is transmitted to anterior cingulate gyrus, the rACC fires back its error messages to the hippocampus, amygdala and the retrosplenial cortex .The retrosplenial cortex⁴² in turn signals the hippocampal complex to correct its input. This unsuccessful attempt to correct the hippocampal-amygdala pairing of emotive and episodic memory leads to a maladaptive state of firing wherein the amygdala readily fires at a lower threshold in its attempt to pair correctly.

The amygdala connects to the hypothalamus via the ventral amygdalofugal pathway and the stria terminalis which ends up in the lateral (controlling thirst and hunger) and ventromedial nuclei (satiety and neuroendocrine control) of the hypothalamus. As a result of signals from the amygdala, the autonomic nervous system is geared for a “fight or flight” reaction and neuroendocrine stress hormones are released.

In the same way that finger deformities or amputations are reflected in its cortical representation through the somatosensory cortex, the hippocampus through the postulated hippocampo-thalamic tract sends multisensory signals of its pathologic state of hippocampal-amygdaloid pairing asynchrony to the parieto-insular vestibular cortex (PIVC). Within a period of 2 months²⁸, when error messages of unsuccessful memory pairings are repeated through the PIVC, a cortical reflection of this pathologic state of maladaptive amygdala firing will be imprinted. Around this 2-month post-trauma period, the manifestations of PTSD in a patient is often clinically detectable.

The vestibulocochlear working concept for PTSD postulates that this repeated process of cortical imprinting of a reorganizing pathological hippocampal-amygdalar pairing and

firing process is behind the intrusive re-experiences of aversive traumatic events – whether in recurring dreams or thoughts by the PTSD sufferer.

VII The Role of Handedness in Locating the Dominant Vestibular Tract

There is a bilateral direct ascending vestibular projection from the vestibular nuclei to the inferior part of the insula, which bypasses the posterolateral thalamus and is stronger in the right hemisphere for right handers^{43 44 45}.

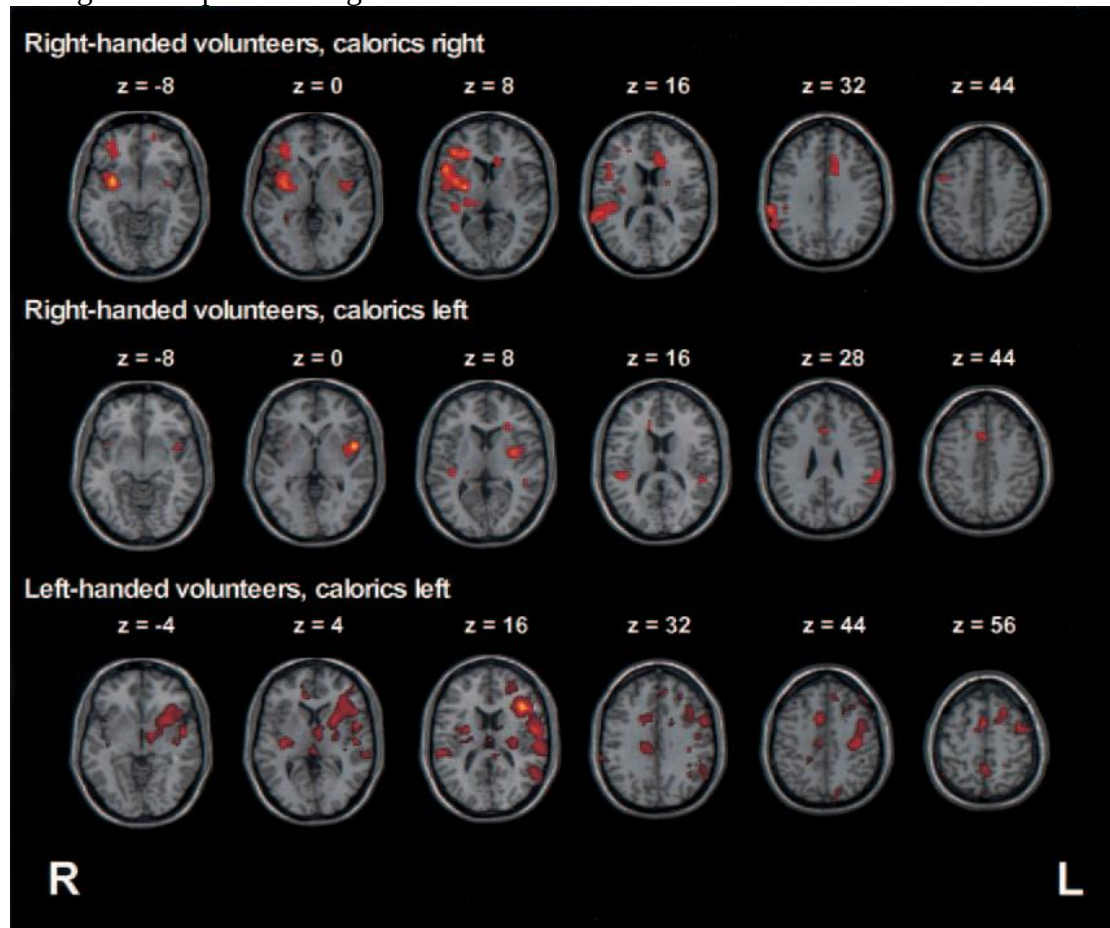


Figure 5. Areas activated during caloric stimulation of the right or left ear in right-handed and left-handed volunteers (group analysis; $n = 12$; $P < 0.001$). Activations were found in, for example, the anterior and posterior insula, the inferior frontal gyrus, the postcentral gyrus, the superior temporal gyrus, the inferior parietal lobule and the anterior cingulum. Note that activations were most pronounced in right-handers during caloric irrigation of the right ear in the right hemisphere and in left-handers during caloric irrigation of the left ear in the left hemisphere. Compared to the activation pattern during caloric irrigation of the right ear, caloric irrigation of the left ear in right-handers led to activations in the temporo-insular and parietal cortex which were smaller in both hemispheres and more frequently located within the left ipsilateral hemisphere.

Earlier blood-flow studies (Dieterich, 2003, 2005)^{43 44} confirmed vestibular dominance in the non-dominant cerebral hemisphere. Knowing that handedness determines the ipsilateral vestibular dominance not only informs us that not all vestibular-impaired

patients will develop PTSD but also clues us further on which vestibular (nerve) – impaired patient would be prone to develop PTSD. Injury to the dominant vestibular tract and a resultant dysfunctional vestibular network sets the stage for PTSD development.

VIII The DSM-IV PTSD criteria explained through the vestibulocochlear theory

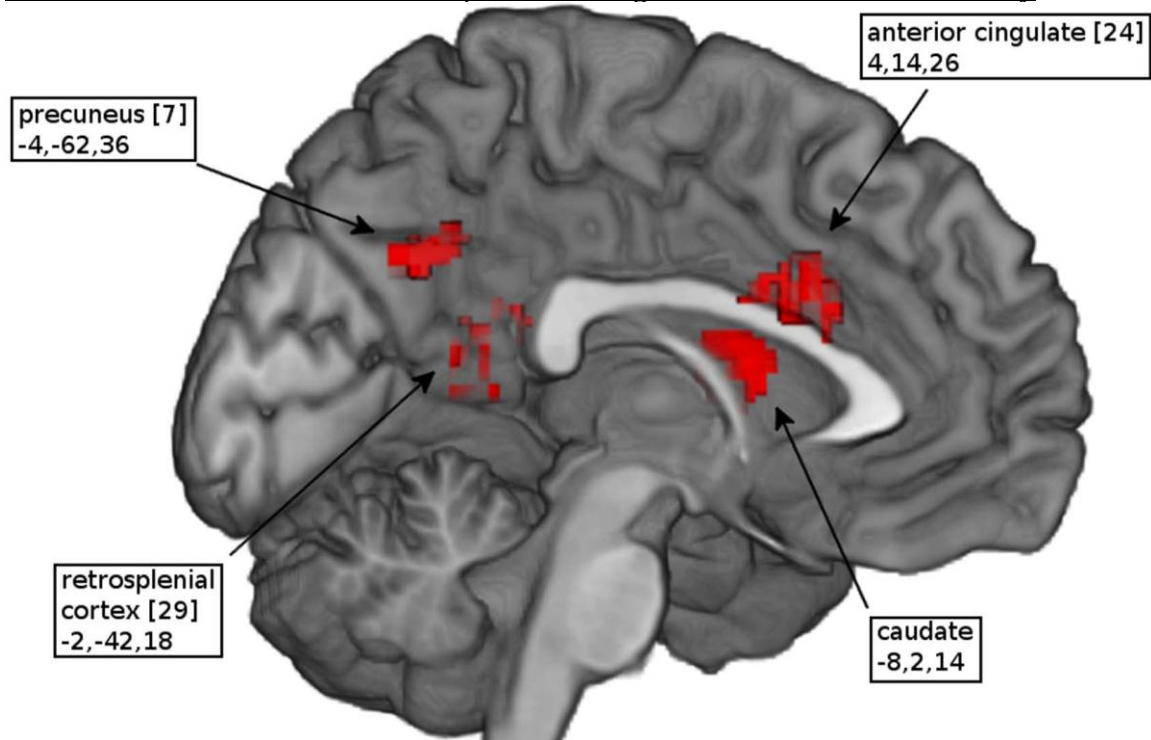


Figure 6. Activation map of patients contrasted with controls. Significant activations of PTSD patients compared to trauma-exposed controls in response to trauma-related stimuli. (Numbers in brackets indicate Brodmann areas and coordinates of the peak voxel are in Talairach space). (Sartory et al, “In Search of Trauma Memory: Meta-Analysis of Functional Neuroimaging in PTSD” *PLOS ONE* 8(3)e58150:1-11, 2013)

DSM-IV PTSD Criteria

Traumatic event

- 1) Emotional memory - The proximity of the auditory cortex to the limbic system enables the encoding of a traumatic event and its storage and retrieval within the adjacent hippocampus. The initial imprint may affect a predisposed individual to allow intrusive recollections or reexperiences of the event. This PTSD manifestation may be traceable to the retrosplenial Cortex^{41 42} or to the build-up of the cortical representation^{7 28} of maladaptive amygdalar firing in PTSD patients.

- 2) exaggerated startle A damaged vestibular apparatus (semicircular canals) detaches from the body the valuable “positioning”

information it needs through the vestibular pathway to allow the appropriate correction to attain balance. As a compensation for this loss, there is heightened use of other senses as touch and vision^{25 26 27}. This compensating hypervigilant state succeeds only in giving an inappropriate exaggerated response causing hyperirritability, insomnia and difficulty in concentration

3) Avoidance

The loss of a normally functioning vestibular system (from vestibular apparatus to hippocampus, meaning from peripheral to higher vestibular functions^{20 21 22 23}) as one of the body's innate defenses leads to a maladaptive and inappropriate approximation of time and space which coupled with heightened compensatory visuo-tactile responses further confuse the PTSD sufferer. This results in withdrawal and generally numbed responses.

4) Social and
Occupational
Dysfunction

There is general depression with clinically significant distress brought about by the presence of sensorineural hearing loss in both or one of the affected ears. There is also impaired higher vestibular function (Navigation²², Self-motion²³, and Global Position sense²¹) which may be distressing if not confusing to the patient. This impairs communication and influences social linkages as well as work productivity.

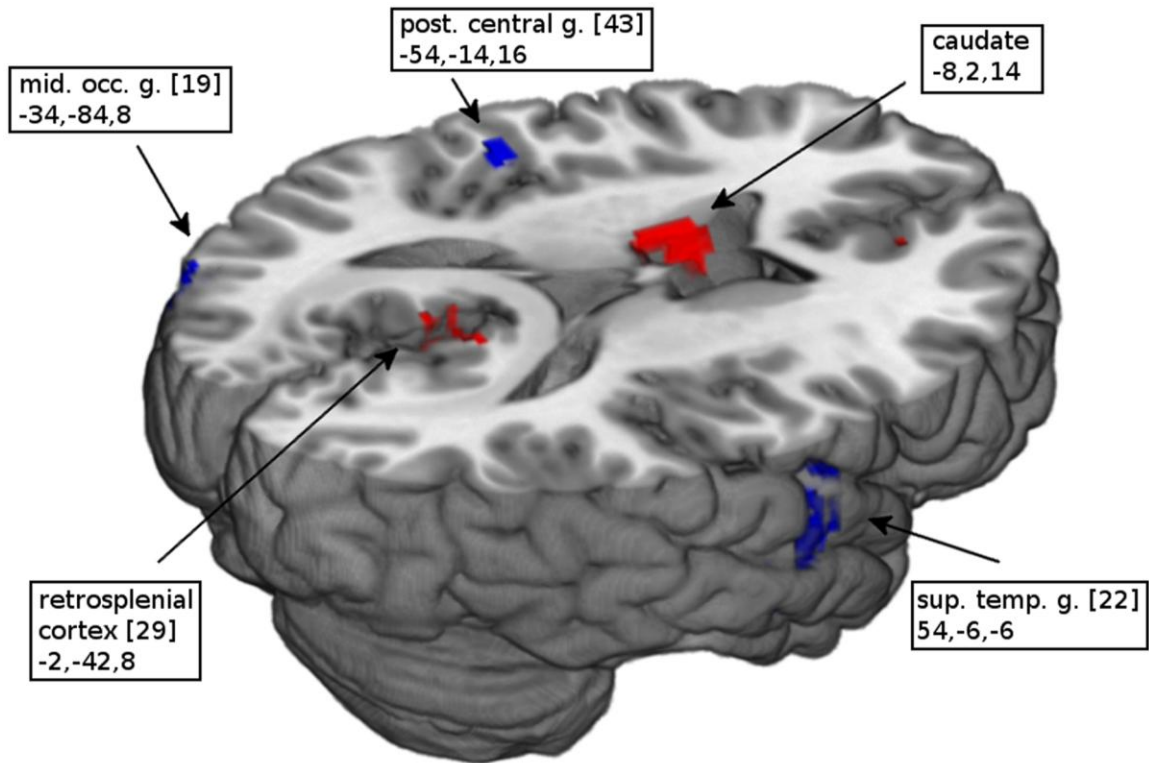


Fig 7 Cross-sectional cut at the level of the midbrain showing the relative locations of the caudate and retrosplenial cortex (red) (Sartory et al, “In Search of Trauma Memory: Meta-Analysis of Functional Neuroimaging in PTSD” *PLOS ONE* 8(3)e58150:1-11, 2013)

IX Implications:

1. Literature-based evidence supports the vestibulocochlear explanation of why amygdalar firing is reset at a lower threshold
2. Impairment of the dominant vestibular pathway determines the manifestation of PTSD in trauma-exposed individuals.
3. The vestibulocochlear concept also explains how PTSD ensues in non-combat (non-Blast injury) situations when ischemia by way of a hypertensive steal effect through the labyrinthine artery ensues to cause functional injury to the vestibular nerve.
4. There may be vestibular disturbances expected for humans exposed to long-term weightlessness in space owing to the gravity-dependence of higher vestibular functions.
5. The vestibulocochlear concept for PTSD complements the neuroendocrine theory of PTSD

X How do we test the vestibulocochlear working concept for PTSD ?

Because of the complexity of Posttraumatic Stress Disorder, there is no suitable animal model to test PTSD. In human subjects, the most minimally invasive means of testing the vestibulocochlear pathway is to use standard of care treatments already in place affecting the auditory, vestibular and compensatory visuo-tactile avenues linked to the vestibulo-auditory pathway. MRI-based neuroimaging (fMRI, DTI and/or HDFT) are also non-invasive and will provide objective criteria when tested on subjects with vestibulocochlear injuries and exhibiting PTSD manifestations.

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